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Applicants	:	Nacamulli et al.
Serial No.	:	09/099,048
Reissue of:	:	U.S. Patent No. 5,527,710
Filed	:	June 17, 1998
For	:	**RATE MEASUREMENTS OF BIOMOLECULAR REACTANTS USING ELECTROCHEMILUMINESCENCE**
Group Art Unit	:	1641
Examiner	:	M. E. Ceperley

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on October 25, 2001

Barry Evans, Reg. No. 22,802
Name of Applicant, ~~Assignee~~ or Registered Representative

Signature

October 25, 2001
Date of Signature

AMENDMENT

Marked up version of claims

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Official Action mailed April 25, 2001, please amend the above-identified application as follows:

IN THE CLAIMS:

37. (Twice Amended) A method for determining the time course of a reaction in which at least one reactant is converted to one or more products, said method comprising:

(a) forming a composition containing [a] said reactant and a luminophore, wherein

(i) the reactant reacts to form a reaction product;

(ii) the luminophore is capable of being induced to emit an electrochemiluminescence signal, wherein electrochemiluminescence emitted by said luminophore is affected by said reaction; and

(iii) the electrochemiluminescence signal emitted upon exposure of said composition to electrical energy changes as the reaction progresses; [and]

(b) exposing the composition to electrical energy at selected [different times] time intervals and measuring the electrochemiluminescence signal during said [different times] selected time intervals to determine the time course of the reaction; and

(c) calculating the time course of the reaction from the ECL signals measured in step (b).

38. (Amended) The method of claim 37, wherein the reaction is a biomolecular reaction of the reactant with a reaction partner.

39. The method of claim 37, wherein the reaction is a binding reaction of the reactant with a reaction partner.

40. The method of claim 37, wherein the reaction is an enzyme catalyzed reaction.

41. (Twice Amended) The method of claim 37, wherein the reactant reacts with the luminophore [in the electrochemiluminescent process].

42. (Twice Amended) The method of claim 37, wherein the reaction product reacts with the luminophore [in the electrochemiluminescent process].

43. The method of claim 37, wherein the reactant is a cofactor.

44. The method of claim 43, wherein the cofactor is NADH.

45. The method of claim 37, wherein the reaction product is a cofactor.

46. The method of claim 45, wherein the cofactor is NADH.

47. The method of claim 37, wherein the luminophore comprises an organic luminophore.

48. The method of claim 37, wherein the luminophore comprises an organometallic luminophore.

49. The method of claim 39, wherein the reactant is an antibody and the reaction partner is an antigen.

50. The method of claim 39, wherein the reactant is attached to the luminophore and the reaction partner is attached to a magnetic bead.

51. The method of claim 37, wherein step (b) comprises exposing the composition to a series of pulses of electrical energy.

52. CANCEL

53. (Amended) The method of claim 37, wherein step (b) [said exposing to electrical energy] comprises exposing the composition to a series of electrical pulses at a preselected potential and at preselected intervals of time and duration.

54. The method of claim 37, further comprising the step of determining the concentration of the reactant in a sample.

55. The method of claim 37, wherein the luminophore is selected from the group consisting of Ru-containing and Os-containing compounds.

56. The method of claim 37, wherein the luminophore is ruthenium tris-bypyridine or osmium tris-bipyridine.

57. (Twice Amended) A method for determining the time course of a binding reaction comprising:

(a) forming a composition containing a reactant, a reaction partner and a luminophore, wherein

(i) the reactant and the reaction partner bind to form a complex;

(ii) the luminophore is capable of being induced to emit an electrochemiluminescence signal; and

(iii) the luminophore is attached to said reaction partner; and

(b) exposing the composition to electrical energy at selected [different times] time intervals and measuring the electrochemiluminescence signal at said time intervals [different times] to determine the time course of the binding reaction.

58. The method of claim 57, wherein the luminophore comprises an organometallic luminophore.

59. The method of claim 57, wherein the reaction partner is an antibody and the reactant is an antigen.

60. The method of claim 57, wherein the reaction partner is attached to the luminophore via a covalent bond.

61. The method of claim 57, wherein the reaction partner is attached to the luminophore via a biotin-streptavidin binding interaction.

62. (Twice Amended) A method for determining the time course of an enzymatic reaction comprising:

(a) forming a composition containing an enzyme, an enzyme substrate and a luminophore, wherein

(i) the enzyme catalyzes the reaction of the substrate to form a reaction product;

(ii) the luminophore is capable of being induced to emit an electrochemiluminescence signal and said electrochemiluminescence signal emitted from said luminophore varies with the concentration of said substrate or said reaction product; and

(iii) the intensity of the electrochemiluminescence signal emitted upon exposure of said composition to electrical energy changes as said reaction progresses; and

(b) exposing the composition to electrical energy at selected [different times] time intervals and measuring the electrochemiluminescence signal at said selected [different times] intervals to determine the time course of the reaction.

63. (Amended) The method of claim 62, wherein the enzyme substrate is a cofactor.

64. The method of claim 63, wherein the cofactor is NADH.

65. (Amended) The method of claim 62, wherein the reaction product is a cofactor.

66. The method of claim 65, wherein the cofactor is NADH.

67. The method of claim 62, wherein the luminophore comprises an organometallic luminophore.

68. (Twice Amended) A method for determining the time course of a reaction comprising:

(a) forming a composition containing a luminophore, a reactant, and a reaction partner of the reactant, wherein the reactant reacts with the reaction partner to form a reaction product; and

(b) exposing the composition to electrical energy at selected [different times] time intervals and measuring the electrochemiluminescence signal at said selected [different times] time intervals to determine the time course of the reaction, wherein the intensity of the electrochemiluminescence signal relates to the concentration of said reactant, said reaction partner of said reactant or said reaction product.

69. (Amended) The method of claim 68, wherein the reaction product is a cofactor.

70. (Amended) The method of claim 69, wherein said luminophore reacts with the reactant, the reaction partner, or the reaction product, to emit an electrochemiluminescence signal upon exposure to electrical energy.

71. The method of claim 57, wherein said luminophore reacts with the reactant, the reaction partner or the reaction product to emit electrochemiluminescence upon exposure to said electrical energy.

72. The method of claim 37, further comprising normalizing said electrochemiluminescence signal.

73. The method of claim 37, further comprising normalizing said electrochemiluminescence signal using a second reaction mixture containing said reactant and said luminophore and wherein said second reaction mixture is allowed to react to completion prior to exposing said second reaction mixture to electrical energy and measuring said emitted electrochemiluminescence signal thereby determining said time course of reaction.

74. The method of claim 38, further comprising normalizing said electrochemiluminescence signal using a blank reactant mixture containing said reactant and said luminophore and not said reaction partner and exposing said blank reactant mixture to electrical energy and measuring emitted electrochemiluminescence signal thereby determining said time course of reaction.

75. The method of claim 74, further comprising normalizing said electrochemiluminescence signal using a second reaction mixture containing said reactant and said luminophore and wherein said second reaction mixture is allowed to react to completion prior to exposing said second reaction mixture to electrical energy and measuring said emitted electrochemiluminescence signal thereby determining said time course of reaction.

Please add the following new claims:

--76. A method for determining the time course of a reaction in a composition containing a luminophore wherein said composition is exposed to electrical energy at selected time intervals during said reaction to induce said luminophore to emit an electrochemiluminescent signal and said electrochemiluminescent signal is measured during said selected time intervals to determine said time course of reaction.

77. The method of claim 76, wherein the reaction is a biomolecular reaction of a reactant with a reaction partner.

78. The method of claim 76, wherein the reaction is a specific binding reaction of a reactant with the reaction partner.

79. The method of claim 76, wherein the reaction is an enzyme catalyzed reaction.

80. The method of claim 76, wherein the reaction is of a reactant to form a reaction product and the concentration of said reactant affects said electrochemiluminescent process.

81. The method of claim 76, wherein the reaction is a reaction of a reactant to form a reaction product and the concentration of said reaction product affects said electrochemiluminescent process.

82. The method of claim 76, wherein the reaction is a reaction of a reactant to form a reaction product and said reactant reacts with said luminophore in the electrochemiluminescence process.

83. The method of claim 76, wherein the reaction is a reaction of a reactant to form a reaction product and said reaction product reacts with said luminophore in the electrochemiluminescence process.

84. The method of claim 76, wherein the reaction is a reaction of a reactant with a reaction partner to form a reaction product and the reactant is an antibody and the reaction partner is an antigen.

85. The method of claim 76, wherein the reaction is a reaction of a reactant with a reaction partner to form a reaction product and the reactant is attached to the luminophore and the reaction partner is attached to a magnetic bead.

86. The method of claim 76, wherein the reaction is a reaction of a reactant to form a reaction product and the reactant is a cofactor.

87. The method of claim 86, wherein the cofactor is NADH.

88. The method of claim 76, wherein the reaction is a reaction of a reactant to form a reaction product and the reaction product is a cofactor.

89. The method of claim 88, wherein the cofactor is NADH.

90. The method of claim 76, wherein the luminophore comprises an organic luminophore.

91. The method of claim 76, wherein the luminophore comprises an organometallic luminophore.

92. The method of claim 76, wherein the luminophore is selected from the group consisting of Ru-containing and Os-containing compounds.

93. The method of claim 76, wherein the luminophore is ruthenium tris-bypyridine or osmium tris-bipyridine.--

REMARKS

Reconsideration and withdrawal of the rejections of the above-identified application are respectfully requested in view of the amendments and remarks herein. All of the issues objected to by the Examiner have been remedied.

Claims 1-75 are pending in this application. Claims 1-36 have been allowed by the Examiner. Claims 37, 41, 42, 53, 57, 62, and 68 have been amended and claim 52 is canceled. New claims 76-93 have been added to more particularly point out and distinctly define the invention. The claims are fully supported in the disclosure of U.S. 5,527,710 (the '710 patent) and are fully enabled. No new matter has been added.

1. Reference to sections of Title 35 U. S. Code.

2. The original patent, or an affidavit or declaration as to the loss or inaccessibility of the original patent, will be submitted before this reissue application is allowed.

3. The Examiner objects to the specification under 37 C.F.R. § 1.71 and rejects claims 37-75 under 35 U.S.C. § 112, first paragraph.

Applicants urge that the present claims are fully supported by and enabled by the specification as originally filed for the reasons set forth in applicant's previous response.

In the Office Action, the Examiner states that the broad generic concept referred to by applicants in their Response dated February 14, 2001 (p. 8) "says nothing about the type of 'biomolecular reaction' contemplated nor anything about how the luminophore is affected or is involved with reaction". Applicants directed the Examiner to this portion of the original disclosure to demonstrate that Applicants had support for the presently claimed subject matter.

Applicants respectfully submit that the present claims are fully supported by and fully enabled by the specification as originally filed. The first paragraph of 35 U.S.C. §112 requires nothing more than objective enablement. Whether this is achieved by illustrative examples or by broad terminology is of no importance. *In re Marzocchi*, 169 U.S.P.Q. 367 (CCPA 1971). An assertion by the Patent Office that the enabling disclosure is not commensurate with the scope of the protection sought must be supported by evidence or reasoning substantiating the doubt so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (CCPA 1974); *In re Bowen*, 181 U.S.P.Q. 48 (CCPA 1974); *In re Armbruster*, 185 U.S.P.Q. 152 (CCPA 1975).

It is improper to reject claims on the ground that the specification does not support the claims when the terms of the claim are no broader than the broadest description of the invention in the specification and there is no reason to challenge the operativeness of the subject matter embraced by the claims. *Ex parte Altermatt*, 183 U.S.P.Q. 436 (POBA 1974).

As stated above, the recitation in col. 2, lines 22-29 of the '710 patent was cited, on page 8 of applicant's February 14, 2001 response, to demonstrate applicants' conception of the generic concept of conducting a biomolecular reaction in the presence of a luminophore,

inducing the luminophore to electrochemiluminesce and determining the time course of reaction by measuring changes in the emitted electrochemiluminescence.

As noted by the Examiner, the subsequent recitations in col. 2 (beginning at line 36) describe specific methods for the determination of the time course of the reaction. However, the broader recitation (col. 2, lines 22-29) indicates that the broad concept of determining the time course of a reaction using multiple ECL measurements was clearly contemplated. The concept is one which, heretofore, was not expected to yield reliable, reproducible and accurate measurements of the time course of reaction.

As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 166 U.S.P.Q. 18, 24 (CCPA 1970). See also, MPEP § 2164.01(b).

One of ordinary skill in the art would be able to practice the presently claimed subject matter in view of the specification and the prior art without undue experimentation. The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 190 U.S.P.Q. 214 (CCPA 1976). See also, MPEP § 2164.01. The fact that experimentation may be complex does not necessarily make it undue if those skilled in the art typically engage in such experimentation. *In re Certain Limited - Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983); *M.I.T. v. A.B. Fortia*, 227 U.S.P.Q. 428 (Fed. Cir. 1985); *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). See also, MPEP § 2164.01.

To assert a rejection for lack of enablement, the Examiner must meet the initial burden of establishing a reasonable basis to question the enablement provided for the claimed invention. *In*

re Wright, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). See also, MPEP §2164.04. The Examiner has failed to present any evidence or reasoning substantiating the allegation that the presently claimed subject matter is not enabled. Accordingly, the burden of proving enablement has not shifted to the Applicants and therefore the rejection is improper.

Even assuming arguendo that a reasonable basis for objecting to the specification was set forth in the Office Action, the description provided in the specification is sufficient to overcome the objection.

Specific examples of biomolecular reactions and how the luminophore may be affected or involved in the reaction are described in the specification. However, the invention should not be not limited to the specific examples described since one of ordinary skill would readily understand that the invention is applicable to biomolecular reactions in general.

Details of the application of ECL time series measurements to enzymatic and affinity binding biomolecular reactions are disclosed in the '710 patent in col. 6 -col. 8 and are illustrative of different types of embodiments of the invention. One of ordinary skill in the art would clearly recognize that as long as the luminophore is affected by the progress of the chemical reaction, measurement of the emitted electochemiluminescence at selected time intervals can be used to determine the time course of the reaction.

One embodiment of the invention relates to methods of determine the time course of reaction for an enzymatic reaction. The '710 patent, col. 6, discloses the reaction mechanism for ECL signal generation for an enzymatic reaction. The luminophore can react with or be affected by the reactants, reactant products, cofactors or any chemical entity that is ECL active. For example, the enzymatic reaction may either produce or consume the ECL active substance, col. 6, lines 35-49, to alter the emitted ECL signal during the application of electrical energy pulses.

Col. 6, lines 50-63, describes the generation of an ECL signal from the interaction of NADH with the Ru-compound. The intensity of the emitted ECL signal will increase with an increased rate of production of NADH or decrease with a decreased rate of production of NADH. If the reaction is consuming NADH, as in the lactate dehydrogenase reaction (col. 7), then the intensity of the ECL signal will decrease with an increased rate of consumption of NADH. The detailed reaction mechanism between the luminophore and the electrode is disclosed in col. 7-8.

Another embodiment of the invention relates to methods of determining the time course of an affinity binding reaction. In affinity binding type of reactions, the luminophore linked to a binding reagent such as an antibody may be reacted with a binding partner such as an antigen that is held in proximity to an electrode, e.g., by magnetic collection of magnetic particles. As the binding reaction proceeds, the ECL active label becomes bound to the magnetic particle and is, thereby, brought into proximity to the electrode, and a rise in the ECL signal occurs (col. 8, lines 39-55).

The use of ECL time series measurement to determine the time course of a reaction is the invention contemplated by the inventors. Applicants submit that the claims are fully supported by and fully enabled by the original specification. However, to further define the invention, claim 37 has been amended to specifically recite the step of "calculating the time course of the reaction from the ECL signals measured in step (b)". Therefore, the claims, as amended, specifically exclude non-enabled processes since the claims are limited to methods which result in the determination of the time course of a reaction. Therefore the claims exclude methods that do not result in the ECL measured time course determination of the evolving chemical moieties in a chemical reaction.

Accordingly, the rejection is improper and should be withdrawn.

4. The Examiner rejects claims 37-75 under 35 U.S.C. § 112, second paragraph. The Examiner states that the specification provides "an enabling written description only of an assay that includes the normalization and calibration steps".

Applicants submit that the present claims are definite and fully enabled pursuant to the first and second paragraphs of 35 U.S.C. 112 for the reasons set forth above. Accordingly, the rejection is improper and should be withdrawn.

5. The Examiner rejects claims 37-75 under 35 U.S.C. § 112, second paragraph, as being indefinite.

Applicants submit that the claims are sufficiently clear and definite pursuant to 35 U.S.C. 112, second paragraph. There are two distinct requirements in 35 U.S.C. §112, second paragraph:

(1) The claims must set forth the subject matter that Applicants regard as their invention; and

(2) The claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.

The first requirement is subjective because it is premised on what the Applicants regard as their invention. The second requirement is objective. It is not evaluated on the basis of the views of the applicant or any particular individual, but rather in the context of whether a claim is definite, i.e., whether the scope of the claim is clear to a hypothetical person of ordinary skill in the relevant art (MPEP, Section 2171).

A claim cannot be rejected solely because of the language used to define the subject matter for which patent protection is sought. *In re Swinehart*, 160 U.S.P.Q. 226 (CCPA 1971). The focus in determining compliance with 35 U.S.C. §112, second paragraph, should be whether

the claims meet the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available (MPEP, Section 2173.02).

Moreover, breadth of a claim is not to be equated with indefiniteness. (MPEP 2173.04). Applicants urge that if the scope of subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends the claim to be of a different scope, then the claim particularly points out and distinctly claims the subject matter which the applicant regards as his invention. *In re Borkowski*, 164 U.S.P.Q. 642 (CCPA 1970); *In re Robins*, 166 U.S.P.Q. 552 (CCPA 1970).

a). In the Office Action, the Examiner asserts the claims do "not further clarify what type of 'reactant' is intended, how it reacts or, in the event of decomposition, how this decomposition product would affect the ECL signal" (Office Action, page 4). Applicants submit that one of ordinary skill in the art would readily understand the meaning of the claims when properly construed in view of the specification. The claims need not be limited to specific reactants and specific reactions as suggested by the Examiner. The claims clearly require a reaction and a luminophore that emits ECL, which ECL is affected by the reaction, which enables the time course of reaction to be determined by measuring the emitted ECL. As described above, this can occur, for example, in an enzymatic reaction or a specific binding reaction. (Applicants note that independent claims 57 and 62 are specifically directed to these embodiments (affinity binding reactions and enzymatic reactions, respectively)). Applicants direct the Examiner's attention to MPEP 2173.04, which clearly states that the "breadth of a claim is not to be equated with indefiniteness". Thus, it is unclear what is the basis for the Examiner's objection. However, to further the prosecution of the application, claim 37 has been amended to more distinctly define the reactant and reaction products and to incorporate

the step of "calculating the time course of reaction from the ECL signals measured". Accordingly, Applicants request that this aspect of the objection be withdrawn.

b). With respect to the objection to claims 37 and 62 as allegedly failing "to specify the same limitations/requirements as are described in" the "examples of operational formats", the claims are sufficiently clear and definite pursuant to 35 USC 112, second paragraph. Applicants submit that there is no reasonable basis set forth in the Office Action for requiring that the claims be limited to the specific "limitations/requirements" described in the specification. It is well established that terms in claims are properly construed in view of the specification and the prior art. The definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. The Examiner's attention is respectfully directed to Section 2173.02 of the MPEP. Applicants also direct the Examiner's attention to MPEP 2173.04, which clearly states that the "breadth of a claim is not to be equated with indefiniteness". Thus, it is unclear what is the basis for the Examiner's objection.

c). With respect to the term "determining said time course of reaction", Applicants urge that the term is sufficiently clear and definite to one of ordinary skill in the art when properly construed in view of the specification. The fact that the claims are not limited to the specific steps described in the specification does not make the term indefinite. Thus, the objection is improper and should be withdrawn.

6. The Examiner rejects claims 37-42, 47, 48, 51-58, 60, 61, 68, and 71-75 under 35 U.S.C. § 112, first paragraph as based on a non-enabling written description.

The amended claims are fully enabled as described in (3) above.

7. Quotation of 35 U.S.C. § 103

8. The Examiner rejected claims 37-75 under 35 U.S.C. § 103 as being obvious over each of references (1) Martin et al (Analytica Chimica Acta 281 (1993), 475-481), Bard et al (U.S. 5,310,687) or Shibue et al (EP 500,305) taken in combination with each of references (2) Karlsson et al (J. Immunological Methods, 145 (1991), 229-240), Sieber (U.S. 4,476,230) or Freundlich et al (U.S. 4,857,454).

Claims 37-75 are not obvious in view of Martin et al., Bard et al., Shibue et al., taken in combination with Karlsson et al., Sieber or Freundlich et al.

The primary references, alone or in combination with the secondary references, fail to teach or suggest the presently claimed invention.

Martin et al. discloses the measurement of glucose with a ruthenium ECL label as described on p. 478. However, the measurements disclosed by Martin do not involve the measurement of the time course of a reaction such as the changing glucose concentration. That is, the results are obtained by using end point measurements. For example, on page 479-480 Martin et al. shows the ECL signal as a function of the glucose concentration and as reported by Martin et al. each point on the curve (fig. 4) is a representation of the mean of three or more injections of a sample. The same sample is not periodically tested over time as the glucose concentration is evolving but is measured once the reaction is complete and the glucose concentration is stable. The electrode sensor then detects the amount of NADH present in the equilibrated solution and a value for the glucose concentration is obtained. Therefore, Martin does not teach or suggest the presently claimed methods of determining the time course of reaction.

Moreover, Martin fails to teach or suggest the surprising and unexpected results achieved using the presently claimed invention. More specifically, one of ordinary skill in the art would have expected that periodic electrical pulses (at preselected intervals) applied to an electrode placed in a solution of the chemical reaction would have caused interference and/or destructive chemical events. The electrochemical effects at the electrode-solution interface would have been expected to consume or damage electroactive species present in solution. Significant error would then be expected to be introduced in obtaining the ECL signal as the chemical reaction progresses over time. Interfering side-reactions and other electrochemical interferences would have been expected to make continuous monitoring of the ECL signal for time course measurements unreliable and inaccurate. There is no suggestion in the prior art that ECL can be used to measure the time course of a reaction.

Bard et al. also fails to teach or suggest the presently claimed invention. Bard is concerned with ECL labels and their methods of attachment for discerning various analyte concentrations. Although Bard et al. uses electrode voltage pulses for ECL generation, Bard fails to teach or suggest that ECL measurements can be made as a chemical reaction is progressing over time to determine time course of reaction. According to Bard, the various analyte concentrations of chemical moieties were determined with ECL in a solution of fixed concentration which respect to the analyte being detected. That is, once the solution equilibrated to the final analyte concentration then the ECL measurement was obtained. As noted by the Examiner (col. 13, lines 56-68) the analyte can involve antibody-antigen reactions. However, no teachings or suggestions were disclosed for a methodology using ECL to determine the time course of the specific binding reactions involving such antibody-antigen reactions.. Applicants submit that prior art ECL methodology avoided or minimized the problem of electrogenerated

consumption or damage to the electroactive species by taking an end point measurement of either the entire reacting solution or isolating small sample solutions from the reacting solution. The one time ECL measurement from the solution taught by Bard does not involve the introduction of significant error from the electrode-solution interface.

In contrast, the present invention involves taking multiple ECL time interval measurements of the entire chemical solution, not a one time or end point measurement of a sample solution. This multiple time series ECL measurement to determine the time course of reaction was not described or suggested by Bard.

Shibue et al. also fails to teach or suggest the presently claimed subject matter. Shibue measures the analyte concentration of chemical moieties which have reached a final equilibrium. Column 1, lines 43-54, describes the process of mixing a liquid sample for the determination of the concentration of an immunoreactant using ECL. It is specifically stated that "an excess of a complementary immunoreactant capable of specifically binding to said immunoreactant to allow an immunoreaction to take place, said complementary immunoreactant having been immobilized on insoluble carrier particles and labeled..." is used (col. 4 lines 46-51). An excess of the complementary component is used to ensure the occurrence of complete reaction. Therefore the measured chemical moiety, immunoreactant, is not in the process of evolving and therefore Shibue is merely taking an end point measurement. A similar recitation is stated in col. 4, lines 35-47, "...the immunoreaction or antigen-antibody reaction between immunoreactant and an excess of an immobilized complementary immunoreactant is allowed to take place...." Shibue does not teach or suggest a method of determining the ECL time course of reaction as presently claimed.

Accordingly, each of the primary references fail to teach or suggest the presently claimed subject matter. The secondary references cited in the Office Action fails to compensate for the deficiencies of the primary references.

The Examiner states that References (2) (Karlsson et al., Sieber or Freundlich et al.) establish that it is well known in the art to monitor the time course (i.e. kinetics) of both antigen-antibody and enzyme-enzyme substrate reactions using conventional analytical methodology.

The prior art does not teach or suggest taking time series ECL measurements to determine the time course of a reaction. In fact, the results achieved in the '710 patent were surprising and unexpected for the reasons set forth above. The prior art does not teach or suggest the surprising and unexpected results achieved using the presently claimed invention.
The cited references (Karlsson et al., Sieber or Freundlich et al.) use optical monitoring of antigen-antibody reactions. However, this is not the same methodology as ECL signal measurements. They are totally different techniques and cannot be compared to ECL procedures for measuring the time course of reaction. The optical methods of the cited references do not introduce electrochemical destructive events while monitoring the reaction. Karlsson et al. uses surface plasmon resonance detection which involves the measurement of the refractive index of transmitted light. Sieber monitors antigen-antibody reactions using optical methods, such as laser, and end point process measurements. Column 2, lines 45-46 state that "Such a process is also known as the end point process." Similarly, Freundlich et al. uses spectrophotometric analysis of preincubated sample solutions to obtain the spectral absorption. No where in any of the references does it indicate that, despite the expected deleterious effects of electrochemiluminescence measurements on a sample, it is still possible to measure the kinetics of a reaction through multiple ECL measurements.

The Examiner states that "In view of the fact that monitoring the time course of antigen-antibody and enzyme-enzyme substrate interactions using conventional analytical techniques is well known in the art (references(2)), it would be obvious to use the well known, equivalent ECL analytical techniques of references (1) for the same purpose, as claimed".

There is no teaching or suggestion in the secondary references cited by the Examiner which would have motivated one of ordinary skill in the art to modify the teachings of the primary references to result in the presently claimed subject matter. Obvious to try is not the standard for determining obviousness (*In re O'Farrell*, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988), *Ecolochem, Inc. v. Southern California Edison Co.*, 56 U.S.P.Q.2d 1065 (Fed. Cir. 2000)). Accordingly, the teachings of the primary references, alone or in combination with the teachings of the secondary references, do not render the presently claimed subject matter unpatentable.

Therefore, the rejection is improper and should be withdrawn.

9. The applicants would like to thank the Examiner for indicating that claims 1-36 have been allowed.

In view of the amendments and remarks herein, the present application is believed to be in condition for allowance. Favorable reconsideration of the application is earnestly solicited. If further issues remain, the Examiner is respectfully requested to call the undersigned attorney.

Respectfully submitted,

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